Oxidative Radical Cyclization of (ω-Iodoalkyl)indoles and Pyrroles. Synthesis of (-)-Monomorine and Three Diastereomers†,‡,§

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Received August 23, 1993•

Addition of excess hydrogen peroxide (10 equiv) to a sonicated solution of $FeSO_4{\cdot}7H_2O$ (1 equiv) in DMSO containing the *N*-(ω-iodoalkyl)indoles **4**, **5**, **11**, and **13** effected oxidative radical cyclization to **6**, **7**, **14**, and **15**, respectively. The (ω-iodoalkyl)pyrroles **21**, **22**, **27**, **38**, and **49** underwent analogous cyclization reactions to **23**, **24**, **28**, **39**, and **50**, respectively. The regiochemistry of these radical cyclization reactions was correctly predicted by FMO calculations in all cases but one. For compound **38**, FMO calculations indicated that radical attack should take place at both C-3 and C-5. Only the product of cyclization at C-5, i.e., **39**, was observed. The enantiomerically pure bicyclic ketone **42**, prepared by the above technique from the iodide **53**, was converted into **55** which, on catalytic reduction (H_2/Rh-Al_2O_3), gave a mixture of (-)-monomorine (**40**) and three of its diastereomers **56**-**58** (see, however, Note Added in Proof).

The intramolecular addition of a radical to an aromatic nucleus followed by oxidation of the new resonance-stabilized radical thus produced back to the aromatic system (oxidative radical cyclization) is a process which has considerable synthetic utility, and several methods have recently been devised to effect such cyclizations. For example, oxidative intramolecular additions to aromatic systems mediated by Mn(III),[1,2] Fe(III),[2] Cu(II),[3] Ce(IV),[2,3] and tri-*n*-butyltin hydride[4,5] which proceed with varying degrees of efficiency have been reported. As a long-term goal, we have been interested in devising efficient and inexpensive methods of effecting oxidative radical cyclization to aromatic systems. In addition, we have been investigating the use of simple computational methods as a possible means of predicting the regioselectivity of such reactions (Artis et al., ref 1). This publication describes some of our recent results in the indole and pyrrole areas.

Dixon et al.[6] showed by EPR spectroscopy that methyl radicals were produced in the reaction of hydroxyl radicals (generated from Ti(III) and hydrogen peroxide) with DMSO. This reaction (eq 1) proceeds in >90% yield based on hydroxyl radicals produced and also can be applied to sulfoxides other than DMSO.[7] Torsell and co-workers[8] demonstrated that methyl radicals could also be efficiently generated from DMSO under Fenton conditions (eq 2) and utilized this process to methylate aromatic and heteroaromatic systems, often in preparatively significant yields (eqs 3-5, R = Me). On the basis of the favorable equilibrium[9] of eq 6,

$$HO^{\bullet} + MeSOMe \rightarrow Me^{\bullet} + MeSO_2H \quad (1)$$

$$MeSOMe + H_2O_2 + Fe(II) \rightarrow Me^{\bullet} + MeSO_2H + Fe(III) + OH^- \quad (2)$$

$$R^{\bullet} + ArH \rightleftarrows [ArHR]^{\bullet} \quad (3)$$

$$[ArHR]^{\bullet} + Fe(III) \rightarrow [ArHR]^{+} + Fe(II) \quad (4)$$

$$[ArHR]^{+} \rightarrow ArR + H^{+} \quad (5)$$

$$Me^{\bullet} + RI \rightleftarrows R^{\bullet} + MeI \quad (6)$$

Minisci et al.[10] showed that the Torsell process, when carried out in the presence of alkyl iodides, could be used to introduce virtually any alkyl group into various basic heteroaromatic systems with impressive efficiency. In addition, Bacchiochi and co-workers very recently utilized this methodology to effect substitution of pyrroles and indoles with electrophilic species such as malonyl, methylmalonyl, (methoxycarbonyl)methyl, cynaomethyl, and perfluoroalkyl radicals.[11] It was surprising to us that the intramolecular version of Minisci's procedure had not been investigated, and therefore we chose to examine the feasibility thereof for the synthesis of bicyclic indoles and pyrroles.

† Contribution no. 881 from the Syntex Institute of Organic Chemistry.

‡ Presented in part at the 74th Canadian Chemical Conference, Hamilton, Ont., Canada, June 2-6, 1991.

§ Dedicated to Dr. John Edwards on the occasion of his retirement after over 30 years of unstinting service to Syntex Research.

‖ Syntex Research Postdoctorate Fellow, 1989-1990.

⊥ A portion of this research was completed by S.J., as a visiting student in these laboratories, in partial fulfillment of the requirements for the degree of Maestria en Ciencias at the Departamento de Química, División de Estudios Superiores, Universidad Nacional Autonoma de México, México, D.F.

• Abstract published in *Advance ACS Abstracts*, April 1, 1994.

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Scheme 1

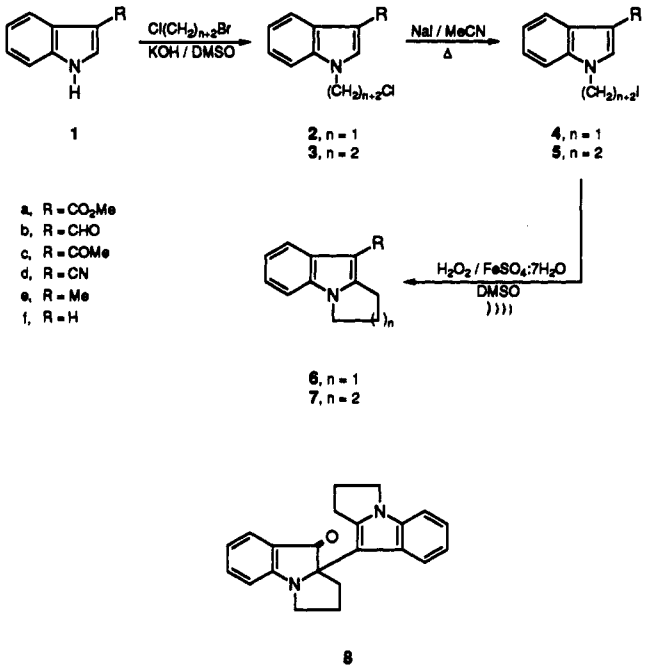
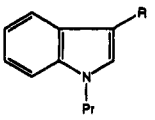


Table 1. Sum of the Squares of the Coefficients of the HOMO's and LUMO's at C-2 and C-7 of 1-Propyl-3-substituted Indoles[a]



R	position	HOMO	LUMO
CHO	2	0.0810	0.3365
	7	0.1573	0.0981
CO_2Me	2	0.0802	0.3322
	7	0.1552	0.1306
COMe	2	0.0821	0.3283
	7	0.1582	0.1095
CN	2	0.0906	0.2990
	7	0.1407	0.1526
Me	2	0.1234	0.2007
	7	0.1249	0.1955
H	2	0.1043	0.1971
	7	0.1498	0.1947

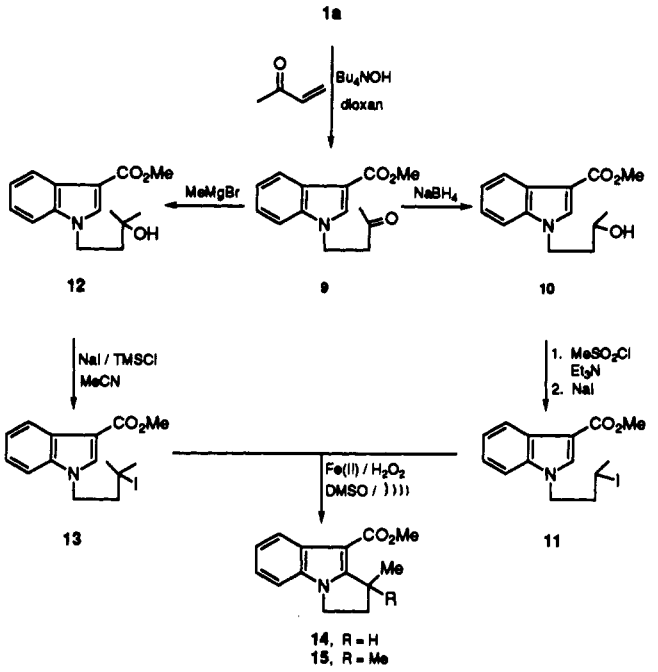
[a] Reference 41.

Results and Discussion

1. Oxidative Radical Cyclization to C-2 of Indoles. The *N*-(ω-iodoalkyl)indole-3-carboxylic acid esters (**4a**, **5a**; Scheme 1) were chosen as model systems for study of the oxidative radical cyclization because Frontier Molecular Orbital (FMO) calculations showed that such compounds have a large LUMO coefficient at C-2 (Table 1) and therefore addition of a nucleophilic radical at this site is expected to be particularly favorable.[12] Indeed, Ziegler and Jeroncic recently reported that radical cyclizations of this type do take place in the presence of tri-*n*-butyltin hydride to give the corresponding dihydro compounds as the major products.[13]

(a) Synthesis of the Starting Materials. The methyl *N*-(ω-iodoalkyl)indole-3-carboxylates **4a** and **5a** (Scheme 1) and the related compounds **4b–f** and **5b–f** were synthesized in two steps by alkylation of the N-unsubstituted indoles **1a–f** with the appropriate α,ω-bromochloroalkane (KOH/DMSO) and subsequent displacement of chloride ion in **2** and **3** with excess sodium iodide in acetonitrile. The secondary and tertiary iodides **11** and **13** (Scheme 2) were prepared from **9**, the conjugate addition product of methyl indole-3-carboxylate (**1a**) to methyl vinyl ketone, via the alcohols **10** and **12**, using standard procedures.

Scheme 2



(b) Cyclization of the *N*-(ω-Iodoalkyl)indoles. Dropwise addition of 30% hydrogen peroxide (3 equiv) to a solution of **4a** and ferrous sulfate heptahydrate (0.3 equiv) in DMSO initiated an exothermic reaction (temperature rose to 80–90 °C) after a short induction period. These reactions ceased to advance when the exotherm had subsided and, in general, the addition of further quantities of peroxide and/or Fe(II) failed to reinitiate them. Although the expected tricyclic compound **6a** was indeed formed, the conversion of **4a** was low (*ca.* 20%). On the assumption that the exotherm was perhaps related to the relatively poor solubility of the ferrous salt in DMSO, solution thereof was effected by brief sonication prior to the addition of hydrogen peroxide. This improved the conversion of **4a** somewhat, but the reactions were still quite capricious in that exotherms often still occurred. After considerable experimentation with the reaction conditions, it was found that the exotherms were always eliminated by sonication during the peroxide addition, and the conversions could be dramatically improved by increasing both the amounts of hydrogen peroxide and $FeSO_4 \cdot 7H_2O$. Thus, addition of hydrogen peroxide (10 equiv) to a sonicated[14] solution of **4a** in DMSO containing 1 equiv of the ferrous salt immediately initiated a mildly exothermic reaction which was easily controlled at *ca.* 40

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(13) Ziegler, F. E.; Jeroncic, L. O. *J. Org. Chem.* **1991**, *56*, 3479.

Table 2. Oxidative Radical Cyclization of N-ω-Iodoalkyl)indoles

starting material	product(s)	% yield	mp, °C observed	mp, °C reported
4a	6a	60–85	81–83	84–86[a]
5a	7a	66	103.5–104.5	123–124[b]
4b	6b	60	146–147	154[c]
5b	7b	45	121–125	
4c	6c	75	156.5–157	
5c	7c	54	133–135	
4d	6d	57[d]	126–127	110–133[a]
5d	7d	48[d]	93–94	
4e	6e	60	oil	48–49[e]
5e	7e	43	oil	15–18[b]
4f	6f	14	75–76	79–80[e]
	8	30	180–183	
5f	7f	38	52–53	52[f]
11	14	80	oil	
13	15	30–34	112–113	
	12	20	oil	
	16	17	oil	
	17	16	oil	

[a] Reference 42. [b] Reference 43. [c] Reference 44. [d] Two equivalents $FeSO_4 \cdot 7H_2O$ required. [e] Reference 45. [f] Reference 46.

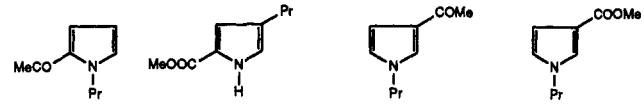
°C by the rate of peroxide addition. In fact, the peroxide addition could be effected quite rapidly (always ≤0.5 h) and upon termination thereof **6a** was always isolated in 60% yield or better. The six-membered compound **7a** was obtained in approximately the same yield from **5a**. Application of this methodology to other 3-substituted congeners of **4a** and **5a**, in all cases except the nitriles **4d** and **5d** (see below), gave the expected cyclization products, usually in quite acceptable yields (Scheme 1 and Table 2). Even the parent members of these series **6f** and **7f** could be prepared in this manner although **6f** was isolated pure in only 13% yield because the crude product (>40% yield) was rapidly converted into an oxygen-containing dimer **8**. The structure of **8** was assigned on the basis of spectroscopic and analytical data as well as by analogy to the well-known[15] air- or peroxide-induced oxidative dimerization products of indoles.

For reasons which we do not understand, the cyclization of the nitriles **4d** and **5d** failed under the standard conditions, but it was successful when the amount of Fe(II) was doubled.

The data given in Tables 1 and 2 indicate that there is no obvious correlation between the LUMO coefficients and the isolated yields of the cyclization products. No correlation was expected since the yields depend on factors subsequent to the radical addition, e.g., product stability under the reaction conditions. It is of interest that when the indole 3-substituent is hydrogen or methyl, the LUMO coefficients for C-2 and C-7 are nearly identical. The observed specificity for C-2 in these cases probably results from the greater energetic cost of breaking resonance in the benzenoid ring over that for the heterocyclic ring. Nevertheless, the data implies that it should be possible to divert the cyclization from C-2 to C-7 for indoles having appropriate substitution in the heterocyclic ring.

The radical cyclization reaction is not restricted to primary iodides. Both the secondary and tertiary alkyl iodides **11** and **13** gave the anticipated products **14** and **15** (Scheme 2 and Table 2) although the latter compound was isolated in modest yield. In this case, the majority of the product consisted of a mixture of the alcohol **12** and the isomeric olefins **16** and **17**, presumably derived from the tertiary carbonium ion corresponding to **13**. The mixture of **12**, **16**, and **17** was also formed in DMSO in the absence of Fe(II) and peroxide. Inasmuch as the generation of such products from *tert*-alkyl iodides in this dipolar aprotic medium is expected to be a common occurrence, oxidative radical cyclization under the conditions described herein is likely to be preparatively useful only for primary and secondary alkyl iodides.

Table 3. Sum of the Squares of the Coefficients of the HOMO's and LUMO's at the Unsubstituted Carbons of Acylated n-Propylpyrroles



A B C D

pyrrole	position	HOMO	LUMO
A	3	0.0832	0.1687
	4	0.1445	0.0001
	5	0.3278	0.1384
B	3	0.0176	0.1850
	5	0.3236	0.1730
C	2	0.3329	0.3383
	4	0.1305	0.0164
	5	0.3820	0.0281
D	2	0.3204	0.3907
	4	0.1400	0.0127
	5	0.3753	0.0366

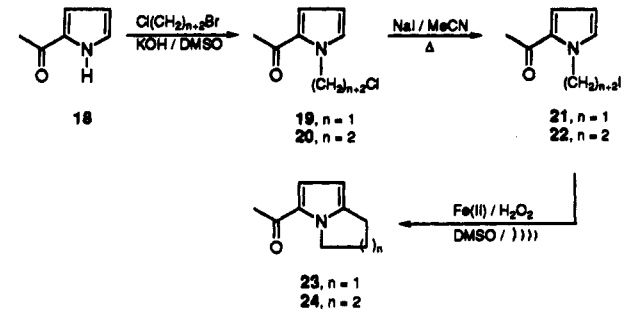
[a] Reference 41.

2. Oxidative Radical Cyclization to Pyrroles. Ghiro[16] has shown that 1-(benzenesulfonyl)-2- or 3-(4-bromobutyryl)pyrroles, on reaction with tri-*n*-butyltin hydride, gave low yields of cyclic products resulting from oxidative radical addition at C-3 and C-2, respectively, with predominant loss of the benzenesulfonyl group.[17] We have recently demonstrated that *N*-(ω-haloalkyl)pyrroles bearing an alkylsulfonyl substituent at C-2 undergo a remarkably facile tri-*n*-butyltin hydride-induced oxidative radical cyclization, usually with loss of the alkylsulfonyl group.[5] In addition, FMO calculations show that acylated pyrroles should be quite susceptible to attack by nucleophilic radicals (Table 3 and Artis et al., ref 1. Unacylated pyrroles do not readily react with such radicals[5]). We, therefore, chose to study the applicability of the oxidative radical cyclization described above to the synthesis of bicyclic pyrrole-containing systems with the intent of applying this methodology to the synthesis of certain indolizidine alkaloids.

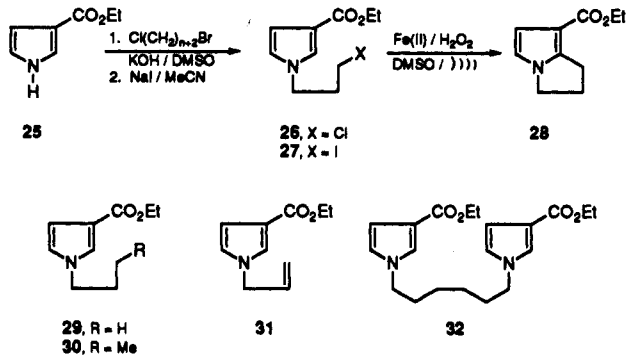
(a) Synthesis of the Starting Materials. The *N*-(ω-iodoalkyl)pyrroles **21**, **22**, and **27** (Schemes 3 and 4) were synthesized from the appropriate acylated pyrroles and the α,ω-bromochloroalkane by the process which was used to prepare the indoles **4** and **5**. Methyl 4-(4-iodopentyl)-pyrrole-2-carboxylate (**38**, Scheme 5) was prepared via a six-step sequence beginning with methyl 1-(*tert*-butoxycarbonyl)-4- bromopyrrole-2-carboxylate (**34**) which in turn was obtained by *tert*-butoxycarbonylation of **33**. The key step in the sequence involved the attachment of a functioned five-carbon chain to C-4 via a palladium(0)-catalyzed coupling[18] of **34** with 2-hydroxy-4-pentyne.

(14) Branson Models CV-6 and 1200 ultrasonic bath type cleaners were used.
(15) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 713.
(16) Ghiro, E. M. Sc. Thesis. Université de Montréal, Oct 1989.
(17) We thank Professor B. Gravel, Departement de chimie, Université de Montréal, for providing us with this information.
(18) Akita, Y.; Ohta, A. *Heterocycles.* **1982**, *19*, 329.

Scheme 3



Scheme 4



Scheme 5

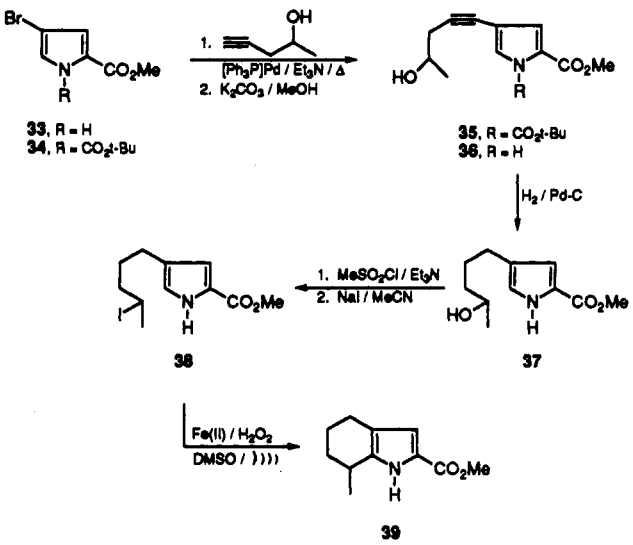


Table 4. Oxidative Radical Cyclization of (ω-Iodoalkyl)pyrroles

starting material	products	% yield
21	23	50
22	24	58
27	28	44–47
	29	8–15
	30	9–11
	31	3–5
	32	5–11
38	39	56–60
49	50	65–75
53	42	63–78

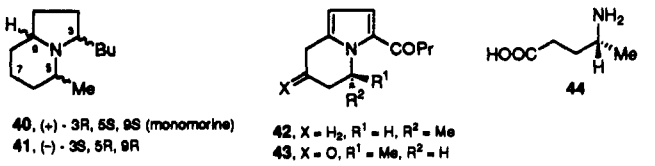
(b) Cyclization of the (ω-Iodoalkyl)pyrroles. Oxidative radical cyclization of **21** and **22** under the usual conditions provided the expected products **23** and **24** in 50 and 58% yields, respectively (Scheme 3 and Table 4). When ethyl *N*-(3-iodopropyl)pyrrole-3-carboxylate (**27**, Scheme 4) was subjected to the standard cyclization conditions, compound **28**, resulting from cyclization at C-2, was the only bicyclic product formed (Table 4). It is noteworthy that where a single site of addition is indicated by FMO calculations to be favored, the observed cyclization products are those predicted in every case examined. The exclusive formation of the more-hindered product **28** from **27** (Scheme 4) and also of **50** from **49** (see below, Scheme 7) is especially interesting in this regard. An analogous result was obtained by Ghiro[16] with 1-(benzenesulfonyl)-3-(4-bromobutyl)pyrrole. The much larger LUMO coefficients at C-2 over C-5 in such systems (C and D in Table 3) suggest that electronic features can play a major role in their reactivity.

A substantial portion of the reaction mixture containing **28** consisted of several noncyclized compounds which were separated by column chromatography and identified by their spectroscopic properties. These byproducts (Scheme 4 and Table 4) must arise from the primary radical corresponding to **27** by processes of disproportionation (**29** and **31**), heterocoupling (**30**, i.e., with the methyl radical), and homocoupling (**32**). One or more of these compounds is formed to a certain extent in all of the radical cyclization reactions described herein.

The cyclization of the secondary radical corresponding to **38** (Scheme 5) was of particular interest because FMO calculations predicted that addition would occur with about equal facility at C-3 and C-5 (Table 3). The sole bicyclic product formed on cyclization of **38** was that which was derived from radical attack at C-5, i.e., **39**. In this case, it may be that when site selectivity is not strongly biased by electronic effects, steric interactions become the dominant factor. Thus, the bulkier secondary radical derived from **38** would cyclize at the sterically less-encumbered α-position.

We had hoped that the radical cyclization could also be applied to benzenoid aromatic systems. Although cyclization of methyl 3-(ω-iodoalkyl)benzoates under the usual conditions did occur to give mixtures of ortho and para products, as predicted by FMO calculations, the product yield were only about 10%. It may be that these cyclizations are more difficult because the activation energy for radical addition to a benzenoid system is higher and/or oxidation of the resulting dienyl radical is a higher energy process.[19]

Scheme 6



(c) Synthesis of (−)-Monomorine. Monomorine (**40**, Scheme 6) is the major alkaloidal component of the pharaoh ant trail pheromone.[23] Total syntheses of this molecule have been reported for the racemic,[24] dextro-[25]

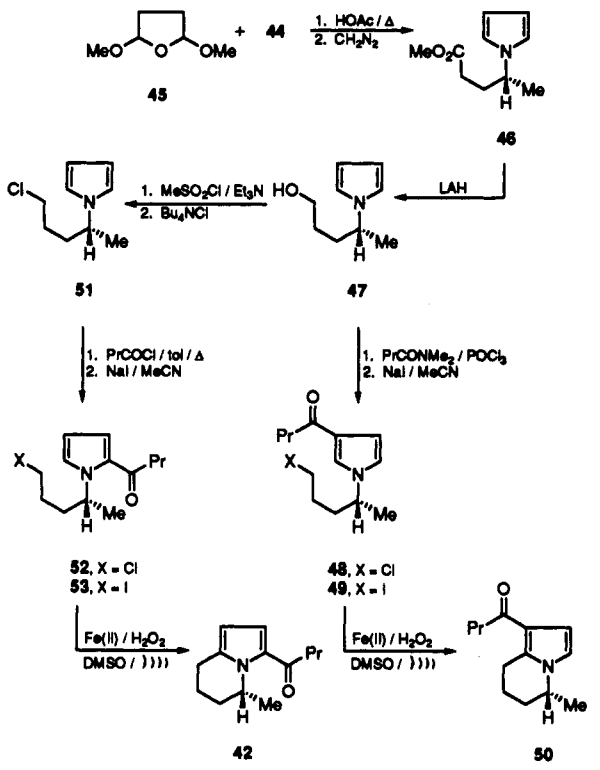
(19) Some support for these speculations is found in the observation that generation of the radicals by phenyl radical abstraction of iodine (benzoyl peroxide/5 mol % $Fe(ClO_4)_2 \cdot 6H_2O$)[20] in acetonitrile at reflux temperature gave the expected meta/para mixtures (1:2) in about 40% yield.[21] The $DMSO/H_2O_2/Fe(II)$ reaction cannot be carried out at temperatures appreciably above 40 °C because the Kornblum oxidation[22] of the iodide to the aldehyde becomes the dominant process.

(20) Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* **1986**, *51*, 4411.

(21) Jaime, S. Unpublished data.

(22) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113.

Scheme 7



and levorotatory[26] forms, the (+)-enantiomer being the naturally occurring substance.

Compound **42** (Scheme 6) was selected as the primary synthetic target enroute to (−)-monomorine, a decision which was greatly influenced by the results of two recent publications. Firstly, Jefford, et al.[27] reported that the palladium-catalyzed hydrogenation of **43** under strongly acidic conditions (10:1 6 N HCl–HOAc) gave (+)-monomorine directly as the major product, a remarkable result indeed. It seemed unlikely to us that the absence of a carbonyl group at C-7 would make the course of the catalytic reduction of **42** significantly different from that of **43**. Secondly, an efficient synthesis of (*R*)-4-aminopentanoic acid (**44**) was recently described by Ohno's group.[28] It was our intention to use this amino acid to introduce the enantiogenic center at C-5, in the first step of the sequence to **42**, by a Clauson-Kaas[29] type of pyrrole synthesis in a manner analogous to that described by Jefford et al.

Condensation of (*R*)-4-aminopentanoic acid (**44**) with dimethoxytetrahydrofuran (**45**, **Scheme 7**) and subsequent esterification with diazomethane gave the 1-substituted pyrrole **46** in *ca.* 70% overall yield. Reduction of **46** with lithium aluminum hydride gave the primary alcohol **47** which was shown by ^{1}H NMR spectroscopy of the Mosher[30] ester to be of >95% enantiomeric purity. A Vilsmeier–Haack reaction of **47** with *N*,*N*-dimethylbutyramide and excess phosphorus oxychloride, in 1,2-dichloroethane at reflux temperature, effected both nuclear acylation and conversion of the alcohol to the chloride. After conversion of the chloride **48** into the iodide **49**, cyclization under the usual conditions gave a single bicyclic product in >70% yield (Table 4). The unexpectedly small coupling constant[31] for the pyrrole protons in the product (J = 3.2 Hz) indicated that the isomeric bicyclic system **50** had been obtained. This problem was traced to the rearrangement of the kinetic product **52** under the acidic conditions of the Vilsmeier–Haack reaction, a previously observed phenomenon.[27,32] This rearrangement was easily obviated by acylation of the chloro compound **51** with excess butyryl chloride in boiling toluene in the absence of a catalyst.[33] The acylated product **52** gave an iodide **53** which in this case cyclized to the required bicyclic ketone **42** (78% yield, Table 4), the ^{1}H NMR spectrum of which showed the expected[31] coupling constant (J = 4.1 Hz) for the pyrrole protons. In addition, consistent with α-acylation, the methine hydrogen was strongly deshielded (≥1.2 ppm) by the carbonyl group in this compound and its acyclic precursors **52** and **53** as compared to the ketone **50** and its precursors **48** and **49**. With the ketone **42** in hand, its hydrogenation to (−)-monomorine under the conditions of Jefford et al. could be examined. We were dismayed to find that this compound was quite unstable in the acidic hydrogenation medium (9:1 6 N HCl–HOAc), being totally destroyed in a few hours even with careful prior deoxygenation (vacuum freeze-thaw technique) of the solvent system. Nevertheless, freshly prepared solutions of the ketone were hydrogenated under the specified conditions (Pd–C, 10 bar H_2, 20 h). A complex mixture, not containing the expected products, was always obtained (see Note Added in Proof).

Because of the failure to achieve the direct reduction of **42** to (−)-monomorine, we were forced to remove the carbonyl group prior to the hydrogenation of the pyrrole ring, even though it was recognized that the directing effect of the chiral center at C-5 would now be insignificant.[34] Compound **42** was converted into the very unstable thioketone **54** (Scheme 8) by the method of Murase et al.[35] and desulfurized to **55** with W-2 Raney nickel. Catalytic hydrogenation of **55** (Rh–Al_2O_2/55 psig/MeOH) gave a mixture (78% yield) which showed four peaks by GLPC with relative areas 33:40:23:3 in order of increasing retention times. Small amounts of each compound were obtained pure by column chromatographic separation of the mixture on alumina. They were readily identified by their spectroscopic properties, especially the highly characteristic ^{13}C NMR spectra, as (−)-monomorine (**40**), **56**, **57**, and **58**, respectively. Compound **40** possessed a negative optical rotation[36] and a ^{13}C NMR spectrum (Table 5) indistinguishable from that reported by Royer and Husson[26] while the ^{13}C spectrum of **57** was identical to that of the frog poison 195B, but its optical rotation (−)

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(25) For a list of the published syntheses of (+)-monomorine, see citations 7 and 8 in Ito and Kibayashi.[24] Angle, S. R.; Breitenbucher, J. G. *Tetrahedron Lett.* **1993**, *34*, 3985.

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Scheme 8

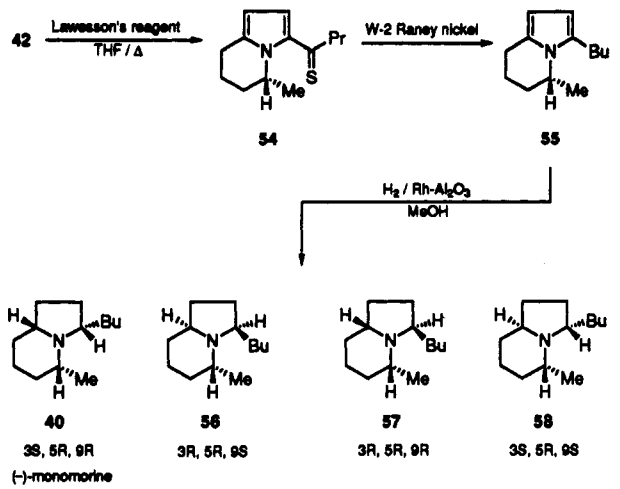

Table 5. Observed and Reported ^{13}C NMR Chemical Shifts for (−)-Monomorine and Diastereomers

(−)-monomorine	56 (3*R*,5*R*,9*S*)	57 (3*R*,5*R*,9*R*)	58 (3*S*,5*R*,9*S*)
14.17 (14.2)[a]	7.53 (7.4)[b]	14.24 (14.2)[c]	14.17 (14.4)[b]
22.90 (22.9)	14.09 (14.3)	20.45 (20.5)	19.03 (19.6)
(23.0)	19.31 (19.8)	23.03 (23.0)	20.52 (20.6)
24.90 (25.1)	23.10 (23.5)	24.72 (24.7)	23.04 (23.5)
29.42 (29.4)	28.19 (28.36)	24.89 (24.9)	26.86 (26.6)
29.76 (29.8)	28.80 (28.44)	26.32 (26.3)	26.94 (27.6)
30.33 (30.5)	29.25 (30.1)	29.18 (29.2)	28.58 (28.9)
30.90 (31.1)	31.58 (32.0)	30.02 (30.0)	28.91 (29.1)
35.83 (36.1)	32.37 (33.1)	32.39 (32.4)	29.10 (29.1)
39.73 (39.8)	32.44 (33.2)	34.52 (34.5)	36.19 (36.4)
60.27 (60.3)	47.33 (47.2)	52.00 (52.0)	48.67 (48.4)
62.91 (63.0)	55.39 (55.4)	58.80 (58.8)	55.29 (55.0)
67.16 (67.3)	59.13 (58.7)	58.96 (59.0)	59.67 (59.4)

[a] Reference 26. [b] Reference 40. Spectrum of the racemate. [c] Reference 37. Spectrum of the 3*R*,5*S*,9*R* compound.

was of opposite sign.[37,38] This base is also described by Royer and Husson who obtained it as a minor product in the synthesis of (−)-monomorine. Compounds **56** and **58** have not been described in the enantiomerically pure forms, but the racemates corresponding thereto were synthesized by Sonnet and Oliver.[39] The ^{13}C NMR spectra reported by Sonnet et al.[40] for the racemic 5*E*,9*Z* and 5*Z*,9*E* isomers closely match those measured for **56** and **58**, respectively.

Summary

An operationally facile and synthetically useful method has been devised for effecting the intramolecular oxidative addition of primary and secondary alkyl radicals to the α-position of indoles and pyrroles. The reaction is carried out in DMSO solution under ultrasonic irradiation and is based on the formation of the radical species by methyl radical abstraction of iodine from the corresponding alkyl iodide in the presence of Fe(III) which serves as the oxidant.[10] The methyl radical in turn is generated, in excess, by the spontaneous β-fragmentation of the DMSO–hydroxyl radical adduct [from H_2O_2 and Fe(II)].[8] The utility of this cyclization reaction was demonstrated by the preparation of the bicyclic ketone **42** which was used to synthesize (−)-monomorine (**40**) and three of its diastereomers (see Note Added in Proof).

It was also shown that simple FMO calculations are of value for the prediction of the regiochemistry of such radical cyclization reactions even though a number of important factors are ignored by this technique. Thus, the energetics of the transition states and the subsequent oxidation steps for the various regioisomers are assumed to be equivalent. Electronic or steric changes which become important after the radical addition are not addressed by this approach. Nevertheless, the agreement between prediction and observation is notable.

Experimental Section

Proton magnetic resonance spectra were recorded at 200, 300, or 500 MHz as $CDCl_3$ solutions and are reported in ppm (δ) downfield from internal tetramethylsilane. The infrared spectra were measured as solutions in $CHCl_3$, as solid dispersions in KBr, or neat as liquid films. See Guzmán, et al.[47] for general information regarding the instrumentation used to obtain the physical constants of the compounds described herein. The spectral data not given below are found in Table VI (supplementary data).

Synthesis of the Chloro Compounds 2a–f, 3a–f, 19, 20, and 26. A mixture of the N-unsubstituted indole or pyrrole (1 equiv), powered 87% KOH (1.3 equiv), and DMSO (20 mL/g of substrate) was sonicated for 10 min and then cooled to 0 °C. The α,ω-bromochloroalkane (3 equiv) was added at 0 °C, and the mixture was then stirred at room temperature for 1–4 h. The reaction mixture was poured into water, the product was extracted into ethyl acetate, and the extract was washed successively with water and saturated sodium chloride solution and then dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel using hexane–ethyl acetate mixtures to elute the product.

Methyl 1-(3-Chloropropyl)indole-3-carboxylate (2a). Eluted from the column with hexane–ethyl acetate (9:1) in 72% yield as an oil: IR (neat) 1700 cm^{-1}; ^1H NMR (300) δ 2.31 (m, 2H, *J* = 6.2 Hz, CH_2), 3.47 (t, 2H, *J* = 6.2 Hz, CH_2Cl), 3.92 (s, 3H, OMe), 4.38 (t, 2H, *J* = 6.2 Hz, NCH_2), 7.25–7.43 (m, 3H, H-5, 6, 7), 7.85 (s, 1H, H-2), 8.16–8.22 (m, 1H, H-4); HRMS calcd for $C_{13}H_{14}ClNO_2$ 251.0713, found 251.0710.

1-(3-Chloropropyl)indole-3-carboxaldehyde (2b). Eluted with hexane–ethyl acetate (7:3) as a solid (94% yield) which had mp 47–48.5 °C after crystallization from ethyl acetate. Anal. Calcd for $C_{12}H_{12}ClNO$: C, 65.02; H, 5.46; N, 6.32. Found: C, 64.83; H, 5.51; N, 6.08.

1-(3-Chloropropyl)-3-acetylindole (2c). Eluted with hexane–ethyl acetate (3:1) in 84% yield as an oil. Anal. Calcd for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.98; N, 5.94. Found: C, 65.88; H, 6.26; N, 5.78.

1-(3-Chloropropyl)-3-cyanoindole (2d). Eluted with hexane–ethyl acetate (85:15) in 83% yield as an oil. Anal. Calcd for $C_{12}H_{11}ClN_2$: C, 65.91; H, 5.07; N, 12.81. Found: C, 65.85; H, 5.40; N, 12.67.

(36) This base (and perhaps **53** as well) has an optical rotation somewhat lower than that reported[26] indicating that some racemization may have occurred during the course of the synthesis (probably in the hydrogenation step).

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(38) The absolute configuration depicted (3*R*,5*R*,9*R*) for alkaloid 195B by these authors[37] is enantiomeric with the correct absolute stereochemistry (i.e., 3*S*,5*S*,9*S*) for this compound.

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(41) Molecular orbital calculations were carried out using the AM1 Hamiltonian as implemented in MOPAC 5.0. The *Z*-matrices were constructed with Sybyl versions 5.41 and 5.5 (Tripos Assoc., St. Louis, MO). MOPAC was used as distributed with these programs. Geometries were fully optimized using the PRECISE keyword.

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(46) For a review, see Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

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1-(3-Chloropropyl)-3-methylindole (2e). Eluted with hexane–ethyl acetate (97:3) in 85% yield as an oil. Anal. Calcd for $C_{12}H_{14}ClN$: C, 69.39; H, 6.79; N, 6.74. Found: C, 69.67; H, 7.10; N, 6.80.

1-(3-Chloropropyl)indole (2f). Eluted with hexane–ethyl acetate (95:5) in 71% yield as an oil: ^1H NMR (300) δ 2.28 (m, 2H, J = 6.2 Hz, CH_2), 3.46 (t, 3H, J = 6.2 Hz, CH_2Cl), 4.35 (t, 2H, J = 6.2 Hz, NCH_2), 6.52 (d, 1H, $J_{2,3}$ = 3.2 Hz, H-3), 7.10–7.16 (m, 1H, H-5), 7.14 (d, 1H, $J_{2,3}$ = 3.2 Hz, H-2), 7.20–7.25 (m, 1H, H-5), 7.38 (dd, 1H, J_o = 8.0 Hz, $J_m \approx$ 1.0 Hz, H-7), 7.65 (d, 1H, $J_o \approx$ 8.0 Hz, H-4); HRMS calcd for $C_{11}H_{12}ClN$ 193.0658, found 193.0658.

Methyl 1-(4-Chlorobutyl)indole-3-carboxylate (3a). Eluted with hexane–ethyl acetate (85:15) in 84% yield as an oil; HRMS calcd for $C_{14}H_{16}ClNO_2$ 265.0870, found 265.0864.

1-(4-Chlorobutyl)indole-3-carboxaldehyde (3b). Eluted with hexane–ethyl acetate (7:3) as a solid (85% yield) which had mp 62–64 °C after crystallization from ethyl acetate. Anal. Calcd for $C_{12}H_{14}ClNO$: C, 66.24; H, 5.98; N, 5.94. Found: C, 66.30; H, 6.15; N, 5.65.

1-(4-Chlorobutyl)-3-acetylindole (3c). Eluted with hexane–ethyl acetate (4:1) in 89% yield as an oil; HRMS calcd for $C_{14}H_{16}ClNO$ 249.0920, found 249.0917.

1-(4-Chlorobutyl)-3-cyanoindole (3d). Eluted with hexane–ethyl acetate (85:15) as a solid (85% yield) which had mp 48–48.5 °C after crystallization from ethyl acetate–hexane. Anal. Calcd for $C_{13}H_{13}ClN_2$: C, 67.09; N, 5.63; N, 12.03. Found: C, 66.96; H, 5.71; N, 11.71.

1-(4-Chlorobutyl)-3-methylindole (3e). Eluted with hexane–ethyl acetate (97:3) in 95% yield as an oil: HRMS calcd for $C_{13}H_{16}ClN$ 221.0971, found 221.0969.

1-(4-Chlorobutyl)indole (3f). Eluted with hexane–ethyl acetate (9:1) in 94% yield as an oil: HRMS calcd for $C_{12}H_{14}ClN$ 207.0815, found 207.0812.

1-(3-Chloropropyl)-2-acetylpyrrole (19). Eluted with hexane–ethyl acetate (9:1) in 93% yield as an oil: ^1H NMR (300) δ 2.20 (m, 2H, J = 6.3 Hz, CH_2), 2.42 (s, 3H, MeCO), 3.45 (t, 2H, J = 6.3 Hz, CH_2Cl), 4.47 (t, 2H, J = 6.3 Hz, NCH_2), 6.14 (dd, 1H, $J_{3,4}$ = 4.08 Hz, $J_{4,5}$ = 2.44 Hz, H-4), 6.92 (t, 1H, H-5), 6.98 (dd, 1H, $J_{3,4}$ = 4.08 Hz, $J_{3,5}$ = 1.71 Hz, H-3); HRMS calcd for $C_9H_{12}ClNO$ 185.0607, found 185.0607.

1-(4-Chlorobutyl)-2-acetylpyrrole (20). Eluted with hexane–ethyl acetate (9:1) in 94% yield as an oil; HRMS calcd for $C_{10}H_{14}ClNO$ 199.0764, found 199.0761.

Ethyl 1-(3-Chloropropyl)pyrrole-3-carboxylate (26). Eluted with hexane–ethyl acetate (4:1) in 91% yield as an oil; IR ($CHCl_3$) 1702 cm^1; ^1H NMR (300) δ 1.32 (t, 3H, J = 7.11 Hz, OCH_2Me), 2.18 (m, 2H, J = 6.2 Hz, CH_2), 3.45 (t, 2H, J = 6.2 Hz, CH_2Cl), 4.08 (t, 2H, J = 6.2 Hz, NCH_2), 4.26 (q, 2H, J = 7.11 Hz, OCH_2Me), 6.57–6.11 (m, 2H, H-4, 5), 7.29 (t, 1H, H-2). Anal. Calcd for $C_{10}H_{14}ClNO_2$: C, 55.68; H, 6.54; N, 6.49. Found: C, 55.74; H, 6.52; N, 6.37.

Synthesis of the Iodo Compounds 4a–f, 5a–f, 21, 22, and 27. A solution of the chloride (1 equiv) in acetonitrile (30 mL/g chloride) containing sodium iodide (3–4 equiv) was heated at reflux temperature for 6–24 h. The solution was poured into water and extracted with ether or dichloromethane. The extract was washed with saturated aqueous sodium sulfite solution and water, and then it was dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel using hexane–ethyl acetate mixtures to elute the product.

Methyl 1-(3-Iodopropyl)indole-3-carboxylate (4a). Eluted with hexane–ethyl acetate (85:15) as a solid (95% yield) which had mp 82.5–83.5 °C after crystallization from ethyl acetate–hexane. Anal. Calcd for $C_{13}H_{14}INO_2$: C, 45.50; H, 4.11; N, 4.08. Found: C, 45.23; H, 4.10; N, 3.74.

1-(3-Iodopropyl)indole-3-carboxaldehyde (4b). Eluted with hexane–ethyl acetate (85:15) in 91% yield as an oil: HRMS calcd for $C_{12}H_{12}INO$ 312.9962, found 312.9962.

1-(3-Iodopropyl)-3-acetylindole (4c). Eluted with hexane–ethyl acetate (85:15) as a solid (95% yield) which had mp 62.5–64 °C after crystallization from ethyl acetate. Anal. Calcd for $C_{13}H_{14}INO$: C, 47.72; H, 4.31; N, 4.28. Found: C, 47.52; H, 4.29; N, 4.20.

1-(3-Iodopropyl)-3-cyanoindole (4d). Eluted with hexane–ethyl acetate (4:1) as a solid (93% yield) which had mp 82–83.5 °C after crystallization from ethyl acetate. Anal. Calcd for $C_{12}H_{11}IN_2$: C, 46.47; H, 3.57; N, 9.03. Found: C, 46.44; H, 3.55; N, 8.77.

1-(3-Iodopropyl)-3-methylindole (4e). Eluted with hexane–ethyl acetate (9:1) in 97% yield as an oil. Anal. Calcd for $C_{12}H_{14}IN$: C, 48.18; H, 4.71; N, 4.68. Found: C, 48.12: H, 4.79; N, 4.69.

1-(3-Iodopropyl)indole (4f). Eluted with hexane–ethyl acetate (98:2) in 88% yield as an oil. Anal. Calcd for $C_{11}H_{12}IN$: C, 46.33, H, 4.24; N, 4.91. Found: C, 46.58; H, 4.35; N, 4.94.

Methyl 1-(4-Iodobutyl)indole-3-carboxylate (5a). Eluted with hexane–ethyl acetate (87:13) as a solid (94% yield) which after crystallization from ethyl acetate had mp 57–60 °C. Anal. Calcd for $C_{14}H_{16}INO_2$: C, 47.07; H, 4.51; N, 3.92. Found: C, 47.38; H, 4.51; N, 4.10.

1-(4-Iodobutyl)indole-3-carboxaldehyde (5b). Eluted with hexane–ethyl acetate (7:3) as a solid (95% yield) which after crystallization from ethyl acetate–hexane had mp 58–59 °C. Anal. Calcd for $C_{13}H_{14}INO$: C, 47.73; H, 4.31; N, 4.28. Found: C, 47.94; H, 4.38; N, 4.26.

1-(4-Iodobutyl)-3-acetylindole (5c). Eluted with hexane–ethyl acetate (7:3) in 98% yield as an oil. Anal. Calcd for $C_{14}H_{16}INO$: C, 49.28; H, 4.73; N, 4.11. Found: C, 49.50; H, 4.85; N, 4.17.

1-(4-Iodobutyl)-3-cyanoindole (5d). Eluted with hexane–ethyl acetate (4:1) as a solid (97% yield) which after crystallization from ethyl acetate–hexane had mp 39.5–40.5 °C. Anal. Calcd for $C_{13}H_{13}IN_2$: C, 48.17; H, 4.04; N, 8.64. Found: C, 48.05; H, 4.01; N, 8.33.

1-(4-Iodobutyl)-3-methylindole (5e). Eluted with hexane–ethyl acetate (95:5) in 91% yield as an oil: HRMS calcd for $C_{13}H_{16}IN$ 313.0326, found 313.0327.

1-(4-Iodobutyl)indole (5f). Eluted with hexane–ethyl acetate (9:1) in 83% yield as an oil: HRMS calcd for $C_{12}H_{14}IN$ 299.0169, found 299.0167.

1-(3-Iodopropyl)-2-acetylpyrrole (21). Eluted with hexane–ethyl acetate (9:1) in 90% yield as an oil. Anal. Calcd for $C_9H_{12}INO$: C, 39.01; H, 4.36; N, 5.05. Found: C, 39.16; H, 4.45; N, 5.13.

1-(4-Iodobutyl)-2-acetylpyrrole (22). Eluted with hexane–ethyl acetate (9:1) in 94% yield as an oil. Anal. Calcd for $C_{10}H_{14}INO$: C, 41.26; H, 4.85; N, 4.81. Found: C, 41.06; H, 4.86; N, 4.75.

Ethyl 1-(3-Iodopropyl)pyrrole-3-carboxylate (27). Eluted with hexane–ethyl acetate (7:3) in 75% yield as an oil. Anal. Calcd for $C_{10}H_{14}INO_2$: C, 39.10; H, 4.59; N, 4.56. Found: C, 39.29; H, 4.67; N, 4.30.

Methyl 1-(3-Oxobutyl)indole-3-carboxylate (9). A solution of methyl indole-3-carboxylate (**1a**, 0.500 g, 2.85 mmol), methyl vinyl ketone (0.600 g, 8.85 mmol), and tetrabutylammonium hydroxide (5 drops, 40 wt % in water) in dioxane (50 mL) was stirred at room temperature in a nitrogen atmosphere for 0.75 h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel (30 g) using hexane–ethyl acetate (4:1) to elute the product (0.525 g, 75% yield) as an oil: IR (neat) 1699, 1535 cm^{-1}; ^1H NMR (300) δ 2.12 (s, 3H, MeCO), 2.97 (t, 2H, J = 6.5 Hz, $COCH_2$), 3.89 (s, 3H, OMe), 4.42 (t, 3H, J = 6.5 Hz, NCH_2), 7.23–7.37 (m, 3H, H-5, 6, 7), 7.85 (s, 1H, H-2), 8.15–8.21 (m, 1H, H-4). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.59; H, 6.27; N, 5.59.

Methyl 1-(3-Hydroxybutyl)indole-3-carboxylate (10). Sodium borohydride (0.038 g, 1 mmol) was added to a stirred solution of the ketone **9** (0.245 g, 1 mmol) in methanol (10 mL), and the solution was stirred for 0.25 h at room temperature. The reaction mixture was poured into 10% hydrochloric acid and the product was extracted with dichloromethane. The extract was dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (25 g) using hexane–ethyl acetate (7:3) to elute the product (0.224 g, 90% yield) which was obtained as an oil: IR (neat) 3446, 1700 cm^{-1}; ^1H NMR (300) δ 1.20 (d, 3H, J = 6.3 Hz, Me), 1.81–2.06 (m, 2H, $CHCH_2$), 3.72 (m, 1H, $CHCH_2$), 3.90 (s, 3H, OMe), 4.24–4.39 (m, 2H, NCH_2), 7.24–7.30 (m, 2H, H-5, 6), 7.38–7.44 (m, 1H, H-7), 7.87 (s, 1H, H-2), 8.14–8.20 (m, 1H, H-4). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.94; N, 5.66. Found: C, 68.00; H, 6.95; N, 5.66.

Methyl 1-(3-Iodobutyl)indole-3-carboxylate (11). Methanesulfonyl chloride (0.137 g, 1.2 mmol) was added at 0 °C to a stirred solution of the alcohol **10** (0.247 g, 1.0 mmol) and triethylamine (0.167 mL, 0.121 g, 1.2 mmol) in dichloromethane (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred for a further 0.5 h at 0 °C and then poured into water. The organic phase was separated, combined with a dichloromethane extract of the aqueous phase, dried over sodium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (10 g) using hexane–ethyl acetate (3:2) to elute the oily product (0.292 g, 91%). This material was used directly in the next step.

The oily mesylate was converted into the iodide using sodium iodide (3 equiv) in acetonitrile in the manner described above for the synthesis of **4a–f**, etc. The crude product was purified by column chromatography on silica gel using hexane–ethyl acetate (9:1) to elute **11** (85% yield) as an oil: IR (neat) 1701 cm^{-1}; ^1H NMR (300) δ 1.93 (d, 3H, J = 6.8 Hz, CH*Me*), 2.05–2.32 (m, 2H, CHCH_2), 3.89–4.00 (m, 1H, *CH*Me), 3.92 (s, 3H, OMe), 4.22–4.45 (m, 2H, NCH_2), 7.25–7.33 (m, 2H, H-5, 6), 7.39–7.45 (m, 1H, H-7), 7.87 (s, 1H, H-2), 8.16–8.21 (m, 1H, H-4); HRMS calcd for $C_{14}H_{16}INO_2$ 357.0224, found 357.0226.

Methyl 1-(3-Hydroxy-3-methylbutyl)indole-3-carboxylate (12). Ethereal methylmagnesium bromide (0.74 mL of a 2.7 M solution, 2.0 mmol) was added dropwise at 0 °C to a stirred solution of the ketone **9** (0.490 g, 2.0 mmol) in dry THF. Stirring at 0 °C was continued for 0.25 h and then the reaction mixture was poured into 10% aqueous ammonium chloride solution. The product was extracted into dichloromethane, and the extract was dried over sodium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (30 g) using hexane–ethyl acetate (7:3) to elute the solid product (0.351 g, 67% yield) which, after crystallization from ethyl acetate–hexane, had mp 79–80.5 °C; IR (KBr) 3444, 1684, 1538 cm^{-1}; ^1H NMR (300) δ 1.32 (s, 6H, Me_2C), 1.99–2.04 (m, 2H, CH_2CMe_2), 3.90 (s, 3H, OMe), 4.28–4.34 (m, 2H, NCH_2), 7.24–7.30 (m, 2H, H-5, 6) 7.37–7.42 (m, 1H, H-7), 7.85 (s, 1H, H-2), 8.14–8.20 (m, 1H, H-4). Anal. Calcd for $C_{15}H_{20}NO_3$: C, 68.67; H, 7.68; N, 5.33. Found: c, 68.31; H, 7.37; N, 5.25.

Methyl 1-(3-Iodo-3-methylbutyl)indole-3-carboxylate (13). The method of Olah et al.[48] was used. Chlorotrimethylsilane (0.253 mL, 0.216 g, 2.0 mmol) was added to a stirred solution of the alcohol **12** (0.262 g, 1.0 mmol) and sodium iodide (0.300 g, 2 mmol) in dry acetonitrile (10 mL) at room temperature. The solution was stirred for 6 h and then poured into 10% aqueous sodium sulfite solution. The product was extracted into dichloromethane, and the extract was dried and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (10 g) using hexane–ethyl acetate (9:1) to elute the solid product (0.320 g, 86%) which, after crystallization from ethyl acetate–hexane, had mp 113–115 °C: IR (KBr) 1686, 1535 cm^{-1}; ^1H NMR (300) δ 2.00 (s, 6H, Me_2C), 2.06–2.11 (m, 2H, CH_2CMe_2), 3.91 (s, 3H, OMe), 4.41–4.46 (m, 2H, NCH_2), 7.27–7.34 (m, 2H, H-5, 6), 7.44–7.47 (m, 1H, H-7), 7.86 (s, 1H, H-2), 8.16–8.19 (m, 1H, H-4). Anal. Calcd for $C_{15}H_{18}INO_2$: C, 48.53; H, 4.88; N, 3.77. Found: C, 48.86; H, 4.89; N, 3.66.

Methyl 1-(*tert*-Butoxycarbonyl)-4-bromopyrrole-2-carboxylate (34). Di-*tert*-butyl dicarbonate (0.262 g, 1.2 mmol) was added to a stirred solution of the bromo compound **33**[49] (0.204 g, 1.0 mmol) and 4-(dimethylamino)pyridine (0.012 g, 0.1 mmol) in acetonitrile at room temperature. Stirring at this temperature was continued for 4 h and the solution was then poured into water. The product was extracted into dichloromethane, and the extract was washed with saturated sodium chloride solution and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (20 g) using hexane–ethyl acetate (9:1) to elute the product (0.212 g, 70% yield) as an oil: IR (neat) 1809, 1757, 1735 cm^{-1}; ^1H NMR (300) δ 1.52 (s, 9H, Me_3C), 3.84 (s, 3H, OMe), 6.79 (d, 1H, J = 1.9 Hz, H-3), 7.30 (d, 1H, J = 1.9 Hz, H-5); MS m/e (rel intensity) 305, 303 (1), 205, 203 (35), 173, 171 (12), 57 (100). Anal. Calcd for $C_{11}H_{14}BrNO_4$: C, 43.43; H, 4.64; N, 4.60. Found: C, 42.98; H, 4.45; N, 4.46.

Methyl 1-(*tert*-Butoxycarbonyl)-4-(4-hydroxypentyn-1-yl)pyrrole-2-carboxylate (35). A solution of the bromo compound **34** (5.00 g, 16.4 mmol), 4-pentyn-2-ol (2.32 mL, 2.07 g, 24.6 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.900 g, 0.82 mmol) in triethylamine (250 mL) was heated at reflux temperature (argon atmosphere) for 5 h. The reaction mixture was poured into water and extracted with dichloromethane, and the extract was dried and evaporated *in vacuo*. The residual mixture was separated by column chromatography on silica gel using hexane–ethyl acetate (9:1) as the eluting solvent. Starting material (2.00 g) was eluted first followed by the product [1.63 g, 32% yield (54%) based on recovered **34**)] as an oil; IR (neat) 3429, 1755, 1733 cm^{-1}; ^1H NMR (300) δ 1.29 (d, 3H, J = 6.1 Hz, *Me*CH), 1.57 (s, 9H, Me_3CO), 2.45–2.61 (m, 2H, CH_2CH), 3.83 (s, 3H, OMe), 3.96–4.06 (m, 1H, CH_2CH), 6.80 (d, 1H, J = 1.8 Hz, H-3), 7.39 (d, 1H, J = 1.8 Hz, H-5); HRMS calcd for $C_{16}H_{21}NO_5$ 307.1420, found 307.1420.

Methyl 4-(4-Hydroxypentyn-1-yl)pyrrole-2-carboxylate (36). A mixture of potassium carbonate (0.138 g, 1.0 mmol) and methanol (50 mL) containing compound **35** (1.54 g, 5.0 mmol) was stirred at room temperature for 12 h. The mixture was poured into water and extracted with dichloromethane, and the extract was dried and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (60 g) using hexane–ethyl acetate (7:3) to elute the solid product (0.770 g, 77% yield) which, after crystallization from hexane–ethyl acetate, had mp 90–91.5 °C; IR (KBr) 3431, 1687, 1568 cm^{-1}; ^1H NMR (300, after D_2O exchange) δ 1.30 (d, 3H, J = 6.2 Hz, *Me*CH), 2.46–2.63 (dq, 2H, CH_2CH), 3.85 (s, 3H, OMe), 3.96–4.04 (m, 1H, CH_2CH), 6.91 (d, 1H, J = 1.4 Hz, H-3), 7.06 (d, 1H, J = 1.4 Hz, H-5). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.75. Found: C, 63.79; H, 6.42; N, 6.37.

Methyl 4-(4-Hydroxypentyl)pyrrole-2-carboxylate (37). A solution of compound **36** (1.00 g, 4.8 mmol) in ethyl acetate (50 mL) containing suspended 10% palladium on carbon catalyst (0.10 g) was hydrogenated at atmospheric pressure until the theoretical amount of hydrogen was consumed. The mixture was filtered through Celite, the filtrate was evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel (200 g) using hexane–ethyl acetate (3:2) to elute the product (0.970 g, 96% yield) which was obtained as an oil: IR (neat) 3320, 1685, 1575 cm^{-1}; ^1H NMR (300) δ 1.19 (d, 3H, J = 6.3 Hz, *Me*CH), 1.44–1.77 (m, 5H, CH_2CH_2CH, OH), 2.49 (t, 2H, J = 7.4 Hz, $CH_2CH_2CH_2CH$), 3.78–3.88 (m, 1H, *CH*Me), 3.83 (s, 3H, OMe), 6.74 (m, 2H, H-3, 5); HRMS calcd for $C_{11}H_{17}NO_3$ 211.1208, found 211.1209.

Methyl 4-(4-Iodopentyl)pyrrole-2-carboxylate (38). The alcohol **37** was converted into the iodide **39** via the mesylate in the same manner as described above for the transformation of **10** to **11**. The crude product was purified by column chromatography on silica gel using hexane–ethyl acetate (9:1) to elute the iodo compound (82% yield from **37**) as an oil: IR (neat) 3316, 1685 cm^{-1}; ^1H NMR (300) δ 1.58–1.87 (m, 4H, CH_2CH_2CH), 1.91 (d, 3H, J = 6.8 Hz, CH*Me*), 2.47–2.52 (m, 2H, $CH_2CH_2CH_2CH$), 3.83 (s, 3H, OMe), 4.16–4.24 (m, 1H, *CH*Me), 6.75 (s, 1H, H-3, 5). Anal. Calcd for $C_{11}H_{16}INO_2$: C, 41.13; H, 5.02; N, 4.36. Found: C, 41.39; H, 5.13; N, 4.24.

General Method for Oxidative Radical Cyclization of the Iodides. To an ultrasonically irradiated[14] solution of ferrous sulfate heptahydrate (1 mol equiv) and the iodide (1 mol equiv) in DMSO (15 mL/mmol iodide) was added 30% hydrogen peroxide (10 mol equiv) dropwise as rapidly as was feasible so that the reaction temperature did not exceed 40 °C. This addition never required more than 0.5 h. The peroxide addition should be effected with a glass delivery system (e.g., a pipette), not via a syringe with a metal needle (many metals catalyze the decomposition of hydrogen peroxide). When the peroxide addition was completed, the reaction mixture was poured into water and extracted with dichloromethane, and the extract was washed with 10% aqueous sodium sulfite solution, dried over sodium sulfate, and evaporated *in vacuo*. The residue was then purified by column chromatography on silica gel or neutral alumina. The yields and melting points, etc. for the indole-

(48) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.
(49) Anderson, H. J.; Lee, S-F. *Can. J. Chem.* **1965**, *43*, 409.

derived products are found in Table 2. The yields of the pyrrole-derived products are given in Table 4.

Methyl 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (6a). Eluted with hexane–ethyl acetate (9:1) as a solid which was crystallized from hexane–ethyl acetate. The ^{1}H NMR spectrum of this compound was identical to that reported by Ziegler and Jeroncic.[13]

2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (6b). Eluted with hexane-ethyl acetate (7:3) as a solid which was crystallized from ethyl acetate. See Table 6 for spectral data (supplementary material).

2,3-Dihydro-9-acetyl-1*H*-pyrrolo[1,2-*a*]indole (6c). Eluted with hexane–ethyl acetate (3:2) as a solid which was crystallized from ethanol: IR (KBr) 1611, 1592, 1518 cm^{-1}; ^{1}H NMR (300) δ 2.51 (s, 3H, COMe), 2.70 (m, 2H, $\sum J$ = 7.4 Hz, 2-CH$_2$), 3.31 (t, 2H, J = 7.6 Hz, 1-CH$_2$), 4.13 (t, 2H, J = 7.2 Hz, 3-CH$_2$), 7.19–7.28 (m, 3H, H-5, 6, 7), 8.24–8.27 (m, 1H, H-8). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: 78.42; H, 6.65; N, 6.85.

2,3-Dihydro-9-cyano-1*H*-pyrrolo[1,2-*a*]indole (6d). Eluted with hexane–ethyl acetate (85:15) as a solid which was crystallized from ethyl acetate. Anal. Calcd for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.37. Found: C, 79.25; H, 5.64; N, 15.23.

2,3-Dihydro-9-methyl-1*H*-pyrrolo[1,2-*a*]indole (6e). Eluted with hexane–ethyl acetate (99:1) as an oil.

2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole (6f) and Compound 8. Compound **6f** was eluted with hexane–ethyl acetate (99:1) as a solid which was crystallized from methanol. The ^{1}H NMR spectrum was identical to that reported by Ziegler and Jeroncic.[13]

Continued elution gave a more-polar solid compound **8** which was further purified by silica gel chromatography using hexane–ethyl acetate (92:8): IR (KBr) 1701, 1612 cm^{-1}; ^{1}H NMR (300) δ 1.99–2.15 (m, 3H), 2.48–2.63 (m, 3H), 2.96–3.06 (m, 1H), 3.16–3.38 (m, 2H), 3.58–3.65 (m, 1H), 3.97–4.02 (m, 2H), 6.87–6.97 (m, 2H), 7.02–7.11 (m, 2H), 7.16–7.19 (m, 1H), 7.51–7.54 (m, 2H), 7.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.04, 27.22, 28.04, 43.18, 50.17, 78.09, 104.01, 109.27, 113.32, 119.04, 120.01, 120.34, 121.08, 123.01, 125.47, 130.42, 132.96, 136.92, 141.77, 164.14, 203.79; MS *m/e* (rel intensity) 328 (100), 299 (87), 271 (78), 258 (22). Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.48; H, 6.13; N, 8.56.

Methyl 1,2,3,4-Tetrahydropyrido[1,2-*a*]indole-10-carboxylate (7a). Eluted with hexane–ethyl acetate (4:1) as a solid which was crystallized from ethyl acetate. Although the mp observed (103.5–104.5 °C) is different from that reported (123–124 °C),[43] the ^{1}H NMR spectrum (Table 6) corresponds well to the published spectrum:[43] HRMS calcd for $C_{14}H_{15}NO_2$ 299.1103, found 299.1100. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.10. Found: C, 73.54; H, 6.55; N, 6.00.

1,2,3,4-Tetrahydropyrido[1,2-*a*]indole-10-carboxaldehyde (7b). Eluted with hexane–ethyl acetate (4:1) as a solid which was crystallized from ethyl acetate–hexane; IR (KBr) 1641, 1609 cm^{-1}; ^{1}H NMR (300) δ 1.94–2.04 (m, 2H, 2-CH$_2$ or 3-CH$_2$), 2.11–2.19 (m, 2H, 3-CH$_2$ or 2-CH$_2$), 3.31 (t, 2H, J = 6.3 Hz, 1-CH$_2$), 4.09 (t, 2H, J = 6.1 Hz, 4-CH$_2$), 7.23-7.34 (m, 3H, H-6, 7, 8), 8.18–8.21 (m, 1H, H-9), 10.15 (s, 1H, CHO). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.38; H, 6.47; N, 7.00.

1,2,3,4-Tetrahydro-10-acetylpyrido[1,2-*a*]indole (7c). Eluted with hexane–ethyl acetate (3:1) as a solid which was crystallized from ethyl acetate–hexane; IR (KBr) 1619 cm^{-1}; ^{1}H NMR (300), 1.89–1.97 (m, 2H, 2-CH$_2$ or 3-CH$_2$), 2.04–2.12 (m, 2H, 3-CH$_2$ or 2-CH$_2$), 2.63 (s, 3H, CH$_3$CO), 3.31 (t, 2H, J = 6.4 Hz, 1-CH$_2$), 4.06 (t, 2H, J = 6.0 Hz, 4-CH$_2$), 7.20–7.31 (m, 3H, H-6, 7, 8), 7.99–8.02 (m, 1H, H-9); HRMS calcd for $C_{14}H_{15}NO$ 213.1154, found 213.1152. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.56. Found: C, 78.46; H, 7.03; N, 6.48.

1,2,3,4-Tetrahydro-10-cyanopyrido[1,2-*a*]indole (7d). Eluted with hexane–ethyl acetate (85:15) as a solid which was crystallized from ethyl acetate: ^{1}H NMR (300) δ 1.93–2.01 (m, 2H, 2-CH$_2$ or 3-CH$_2$), 2.10–2.17 (m, 2H, 3-CH$_2$ or 2-CH$_2$), 3.12 (t, 2H, J = 6.4 Hz, 1-CH$_2$), 4.08 (t, 2H, J = 6.1 Hz, 4-CH$_2$), 7.22–7.33 (m, 3H, H-6, 7, 8), 7.65–7.68 (m, 1H, H-9). Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.53; H, 6.18; N, 14.17.

1,2,3,4-Tetrahydro-10-methylpyrido[1,2-*a*]indole (7e). Eluted from the alumina column (act. II) with hexane as an oil: ^{1}H NMR (300) δ 1.86–1.94 (m, 2H, 2-CH$_2$ or 3-CH$_2$), 2.02–2.09 (m, 2H, 3-CH$_2$ or 2-CH$_2$), 2.88 (t, 2H, J = 6.4 Hz, 1-CH$_2$), 4.02 (t, 2H, J = 6.1 Hz, 4-CH$_2$), 7.06–7.16 (m, 2H, J_o = 7.1 Hz, J_m = 1.6 Hz, H-7, 8), 7.23 (dd, 1H, J_o = 7.1 Hz, J_m = 1.6 Hz, H-6), 7.49 (dd, 1H, J_o = 7.1 Hz, J_m = 1.6 Hz, H-9). Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.11; H, 8.17; N, 7.53.

1,2,3,4-Tetrahydro-pyrido[1,2-*a*]indole (7f). Eluted from the alumina column (act. III) with hexane as a solid which was crystallized from methanol.

Methyl 1-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (14). Eluted with hexane–ethyl acetate (4:1) as an oil: IR (neat) 1697, 1546 cm^{-1}; ^{1}H NMR (300) δ 1.43 (d, 3H, J = 7.1 Hz, 1-Me), 2.22–2.30 (m, 1H, H-2), 2.78–2.91 (m, 1H, H-2′), 3.68–3.76 (m, 1H, H-1), 3.90 (s, 3H, OMe), 4.08–4.15 (m, 2H, 3-CH$_2$), 7.20-7.26 (m, 3H, H-5, 6, 7), 8.09–8.13 (m, 1H, H-8). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.33; H, 6.59; N, 6.11. Found: C, 73.39; H, 6.57; N, 6.15.

Methyl 1,1-Dimethyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (15), and Methyl 1-(3-Methyl-3-buten-1-yl)-indole-3-carboxylate (16), and Methyl 1-(3-Methyl-2-buten-1-yl)indole-3-carboxylate (17). The crude product obtained in the usual way was separated by column chromatography on silica gel using hexane–ethyl acetate (95:5). The order of elution was **15**, **17**, **16**, and **12**.

Compound **15** was obtained as a solid which was crystallized from methanol: IR (KBr) 1684, 1535 cm^{-1}; ^{1}H NMR (300) δ 1.58 (s, 6H, CMe$_2$), 2.48 (t, 2H, J = 7.07 Hz, 2-CH$_2$), 3.92 (s, 3H, OMe), 4.11 (t, 2H, J = 7.07 Hz, 3-CH$_2$), 7.20–7.26 (m, 3H, H-5, 6, 7,), 8.10–8.16 (m, 1H, H-8). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.75. Found: C, 73.72; H, 6.96; N, 5.41.

Compound **17** was obtained as an oil: ^{1}H NMR (300) δ 1.80 [d, 3H, J = 0.8 Hz, CH = C*Me*(c)], 1.83 [s, 3H, CH = C*Me*(t)], 3.91 (s, 3H, OMe), 4.70 (d, 2H, J = 7.0 Hz, NCH$_2$), 5.38–5.42 (m, 1H, *CH*=CMe$_2$), 7.25–7.30 (m, 2H, H-5, 6), 7.34–7.38 (m, 1H, H-7), 7.83 (s, 1H, H-2), 8.14–8.19 (m, 1H, H-4). This compound was not characterized further.

Compound **16** was obtained as an oil: ^{1}H NMR (300) δ 1.78 (bs, 3H, CMe), 2.56 (t, 2H, J = 7.5 Hz, NCH$_2$ *CH$_2$*), 3.91 (s, 3H, OMe), 4.26 (t, 2H, J = 7.5 Hz, NCH$_2$), 4.68 (m, 1H, C=CH$_2$), 4.83 (m, 1H, C=CH$_2$), 7.26–7.32 (m, 2H, H-5, 6), 7.37–7.40 (m, 1H, H-7), 8.16–8.19 (m, 1H, H-4). This compound was not further characterized.

5-Acetyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole (23). Eluted with hexane–ethyl acetate (9:1) as a solid which, on crystallization from methanol, had mp 39.5–41.5 °C; ^{1}H NMR (300) δ 2.35 (s, 3H, MeCO), 2.49 (m, 2H, $\sum J$ = 7.4 Hz, 2-CH$_2$), 2.82 (t, 2H, J = 7.5 Hz, 1-CH$_2$), 4.29 (t, 2H, J = 7.2 Hz, 3-CH$_2$), 5.87 (d, 1H, J = 3.9 Hz, H-7), 6.91 (d, 1H, J = 3.9 Hz, H-6). Anal. Calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.68; H, 7.65; N, 9.29.

3-Acetyl-5,6,7,8-Tetrahydropyrrolo[1,2-*a*]pyridine (24). Eluted with hexane–ethyl acetate (9:1) as an oil: ^{1}H NMR (300) δ 1.74–1.82 (m, 2H, 6-CH$_2$ or 7-CH$_2$), 1.89–1.97 (m, 2H, 7-CH$_2$ or 6-CH$_2$), 2.37 (s, 3H, MeCO), 2.81 (t, 2H, J = 6.3 Hz, 8-CH$_2$), 4.37 (t, 2H, J = 6.1 Hz, 5-CH$_2$), 5.88 (d, 1H, J = 4.07 Hz, H-1), 6.92 (d, 1H, J = 4.07 Hz, H-2); HRMS calcd for $C_{10}H_{13}NO$ 163.0997, found 163.1001.

Ethyl 1,2-Dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-7-carboxylate (28), Ethyl 1-Propylpyrrole-3-carboxylate (29), Ethyl 1-Butylpyrrole-3-carboxylate (30), Ethyl 1-(2-propen-1-yl)-pyrrole-3-carboxylate (31) and Dimer (32). The crude product obtained in the usual way was separated by column chromatography on silica gel using hexane–ethyl acetate (9:1). The order of elution was **30**, **29**, **31**, **28**, and **32**. All the compounds were obtained as oils.

Compound **30**: IR (neat) 1729 cm^{-1}; ^{1}H NMR (300) δ 0.92 (t, 3H, J = 7.3 Hz, CH$_2$*CH$_3$*), 1.27–1.36 (m, 2H), 1.32 (t, 3H, J = 7.1 Hz, OCH$_2$*CH$_3$*), 1.68–1.80 (m, 2H), 3.85 (t, 2H, J = 7.1 Hz, NCH$_2$), 4.26 (q, 2H, J = 7.2 Hz, O*CH$_2$*CH$_3$), 6.51–6.61 (m, 2H, H-4, 5), 7.26 (t, 1H, H-2); MS *m/e* (rel intensity) 195 (92), 153 (95), 150 (100), 80 (68). Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.65; H, 8.77; N, 7.17. Found: C, 67.53; H, 8.73; N, 7.12.

Compound **29**: ^{1}H NMR (300) δ 0.88 (t, 3H, J = 7.4, CH$_2$*CH$_3$*), 1.31 (t, 3H, J = 7.2 Hz, OCH$_2$*CH$_3$*), 1.71–1.83 (m, 2H, $\sum J$ = 7.2

Hz, CH_2CH_3), 3.80 (t, 2H, J = 7.0 Hz, NCH_2), 4.24 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 6.55 (m, 2H, H-4, 5), 7.26 (t, 1H, H-2). This compound was not further characterized.

Compound **31**: ^{1}H NMR (300) δ 1.32 (t, 3H, J = 7.2, OCH_2CH_3), 4.45–4.48 (2H, N-CH_2), 5.11–5.26 (m, 2H, CH=CH_2), 5.87–5.98 (m, 1H, CH=CH_2), 6.57 (m, 2H, H-4, 5), 7.27 (m, 1H, H-2). This compound was not characterized further.

Compound **28**: HRMS calcd for $C_{10}H_{15}NO_2$ 179.0946, found 179.0947. This is a known compound. Its IR, MS, and ^{1}H NMR spectral data are in excellent agreement with those reported.[50]

Compound **32**: IR (neat) 1700, 1543 cm^{-1}; ^{1}H NMR (300) δ 1.23–1.30 (m, 4H), 1.32 (t, 6H, J = 7.2 Hz, OCH_2CH_3), 1.68–1.76 (m, 4H), 3.82 (t, 4H, J = 6.9 Hz, NCH_2), 4.25 (q, 4H, J = 7.2 Hz, OCH_2CH_3), 6.55 (m, 4H, H-4, 4′, 5, 5′), 7.24 (t, 2H, H-2, 2′); HRMS calcd for $C_{20}H_{28}N_2O_4$ 360.2049, found 360.2051.

Methyl 4,5,6,7-Tetrahydro-7-methylindole-2-carboxylate (39). Eluted with hexane–ethyl acetate (95:5) as a solid which, on crystallization from methanol, had mp 93–95 °C; IR (KBr) 1684 cm^{-1}; ^{1}H NMR (300) δ 1.24 (d, 3H, J = 7.0 Hz, *Me*CH), 1.35–1.46 (m, 1H), 1.57–1.70 (m, 1H), 1.87–1.98 (m, 2H), 2.47–2.51 (m, 2H), 2.78–2.88 (m, 1H, Me*CH*), 3.82 (s, 3H, OMe), 6.63 (s, 1H, H-3). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.24. Found: C, 68.24; H, 7.97; N, 7.12.

(*R*)-Methyl 1-[4-(Methoxycarbonyl)butan-2-yl]pyrrole (46). Dimethoxytetrahydrofuran (1.83 mL, 1.87 g, 14.2 mmol) was added over a 10-min period to a boiling solution of (*R*)-4-aminopentanoic acid (1.30 g, 11.1 mmol) and sodium acetate (5.46 g, 66.6 mmol) in acetic acid (10 mL). The solution was maintained at reflux temperature for a further 0.33 h and then it was poured into water. The solution was exhaustively extracted with ethyl acetate (≥five times), and the extract was dried over sodium sulfate and evaporated *in vacuo*. The residue was taken up in ether and treated with excess ethereal diazomethane, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate (9:1) to elute the product (1.37 g, 68%) as an oil; $[\alpha]^{20}_D$ −34.2° (*c* 1.02, MeOH); IR ($CHCl_3$) 1733 cm^{-1}; ^{1}H NMR (200) δ 1.48 (d, 3H, J = 6.8 Hz, *Me*CH), 1.90–2.20 (m, 4H, CH_2CH_2), 3.65 (s, 3H, OMe), 4.01–4.20 (m, 1H, Me*CH*), 6.15 (t, 2H, H-3, 4), 6.68 (t, 2H, H-2, 5). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.72. Found: C, 66.12; H, 8.31; N, 7.67.

The ^{1}H NMR (500 MHz) spectrum of the Mosher ester (*R*) of the racemate showed a pair of doublets of δ 1.400 and 1.407 for the secondary methyl group α to the pyrrole N-atom. The Mosher ester of the (*R*)-(−)-compound showed the low-field doublet with only a trace (≪5%) of the high-field absorption.

(*R*)-1-(5-Hydroxypentan-2-yl)pyrrole (47). A solution of the ester **46** (0.730 g, 4.02 mmol) in dry ether (10 mL) was added to a stirred suspension of lithium aluminum hydride (0.153 g, 4.02 mmol) in ether (50 mL) at 10 °C. Stirring at this temperature was continued for a further 10 min and then water (0.2 mL) was added slowly and the temperature was left to reach ambient. The mixture was filtered through Celite, the filtrate was evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel (50 g). The product (0.573 g, 93% yield) was eluted with hexane–ethyl acetate (7:3) as an oil; $[\alpha]^{20}_D$ −21.45° (*c* 1.10, MeOH); IR ($CHCl_3$) 3624, 3484 cm^{-1}; ^{1}H NMR (200) δ 1.26–1.58 (m, 2H, $HOCH_2CH_2$), 1.47 (d, 3H, J = 6.8 Hz, *Me*CH), 1.81 (q, 2H, $\sum J$ = 7.6 Hz, CH_2CHMe), 3.59 (t, 2H, J = 6.3 Hz, $HOCH_2$), 4.06 (m, 1H, $\sum J$ = 7.1 Hz, Me*CH*), 6.16 (t, 2H, H-3, 4), 6.71 (t, 2H, H-2, 5); HRMS calcd for $C_9H_{15}NO$ 153.1154, found 153.1153.

(*R*)-1-(5-Chloropentan-2-yl)-3-*n*-butyrylpyrrole (48). Phosphoros oxychloride (1.94 mL, 3.50 g, 22.8 mmol) was added slowly at 0 °C to a stirred solution of *N*,*N*-dimethylbutyramide (2.91 mL, 2.39 g, 20.8 mmol) in dry 1,2-dichloroethane (5 mL). When the addition was completed, the solution was left to reach room temperature (N_2 atmosphere) and after 0.5 h it was cooled to 0 °C and the alcohol **47** (1.52 g, 9.9 mmol) was added. The solution was left to reach ambient temperature and then it was heated at reflux for 0.5 h. The solution was cooled to 10 °C, a solution of sodium acetate (22 g) in water (30 mL) was added carefully and the mixture was heated at reflux temperature for 0.33 h. The mixture was poured onto ice, the product was extracted into ether, and the extract was washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (50 g) using hexane–ether (4:1) to elute the product (1.57 g, 64% yield) as an oil: $[\alpha]_D^{20}$ −20.1° (*c* 1.01, MeOH); IR ($CHCl_3$) 1652 cm^{-1}; ^{1}H NMR (200) δ 0.97 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.49 (d, 3H, J = 6.8 Hz, *Me*CH), 1.56–1.98 (m, 6H), 2.70 (t, 2H, J = 7.4 Hz, $COCH_2$), 3.39–3.58 (m, 2H, CH_2Cl), 3.98–4.14 (m, 1H, Me*CH*), 6.58 (m, 1H, H-4 or H-5), 6.61 (m, 1H, H-5 or H-4), 7.32 (m, 1H, H-2). Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.58; H, 8.33; N, 5.79. Found: C, 64.23; H, 8.32; N, 5.75.

(*R*)-1-(5-Iodopentan-2-yl)-3-*n*-butyrylpyrrole (49). Synthesized in the manner described for **4a–f**, etc. in 76–86% yield. The crude product was purified by column chromatography on silica gel using hexane–ethyl acetate (4:1) to elute **49** as an oil. Anal. Calcd for $C_{13}H_{20}INO$: C, 46.85; H, 6.05; N, 4.20. Found: C, 46.81; H, 6.08; N, 4.18.

(*R*)-1-*n*-Butyryl-5-methyl-5,6,7,8-tetrahydropyrrolo[1,2-*a*]pyridine (50). The general procedure was used to effect the oxidative radical cyclization of **49** to **50** (65–75% yield). The crude product was purified by column chromatography on silica gel using hexane–ethyl acetate (9:1) to elute **50** as an oil; $[\alpha]^{20}_D$ −13.83° (*c* 1.05, MeOH); IR ($CHCl_3$) 1642 cm^{-1}; ^{1}H NMR (200) δ 0.97 (t, 3H, J = 7.4 Hz, CH_2CH_3), 1.47 (d, 3H, J = 6.4 Hz, *MeCH*), 1.59–2.12 (m, 6H), 2.69 (t, 2H, J = 7.5 Hz, $COCH_2$), 2.92–3.28 (m, 1H, H-8), 4.02–4.18 (m, 1H, Me*CH*), 6.54 (d, 1H, J = 3.2 Hz, H-4 or H-5), 6.58 (d, 1H, J = 3.2 Hz, H-5 or H-4); MS *m*/*e* (rel intensity) 205 (25), 162 (100). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75,46; H, 9.16; N, 6.63.

(*R*)-1-(5-Chloropentan-2-yl)pyrrole (51). Methanesulfonyl chloride (0.72 mL, 1.08 g, 9.4 mmol) was added at 0 °C to a stirred solution of the alcohol **47** (1.20 g, 7.8 mmol) and triethylamine (1.63 mL, 1.19 g, 11.8 mmol) in dry dichloromethane (25 mL) and stirring at 0 °C was continued for a further 0.33 h. The solvent was removed *in vacuo*, the residue was dissolved in dry acetonitrile, and tetra-*n*-butylammonium chloride (6.53 g, 23.5 mmol) was added. The solution was stirred at room temperature for 6 h and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (200 g) using hexane–ethyl acetate (9:1) to elute the product (1.17 g, 87% yield) as an oil; $[\alpha]^{20}_D$ −20.6° (*c* 1.04, MeOH); ^{1}H NMR (200) δ 1.20–2.02 (m, 4H), 1.47 (d, 3H, J = 6.8 Hz, *Me*CH), 3.36–3.53 (m, 2H, CH_2Cl), 3.95–4.12 (m, 1H, Me*CH*), 6.15 (t, 2H, H-3, 4), 6.70 (t, 2H, H-2, 5). This compound was not characterized further.

(*R*)-1-(5-Chloropentan-2-yl)-2-butyrylpyrrole (52). A solution of the chloro compound **51** (1.10 g, 6.4 mmol) and butyryl chloride (3.32 mL, 3.4 g, 32 mmol) in anhydrous toluene (25 mL) was heated at reflux temperature for 72 h and the solvent was then removed *in vacuo*. The residue was purified by column chromatography on silica gel (50 g) using hexane–ethyl acetate (95:5) to elute the product (0.975 g, 63% yield) as an oil; $[\alpha]^{20}_D$ 16.3° (*c* 1.3, MeOH); IR ($CHCl_3$) 1644 cm^{-1}; ^{1}H NMR (200) δ 1.00 (t, 3H, J = 7.4 Hz, *Me*CH_2), 1.44 (d, 3H, J = 6.6 Hz, *Me*CH), 1.52–1.94 (m, 6H), 2.78 (t, 2H, J = 7.5 Hz, $COCH_2$), 3.41–3.50 (m, 2H, CH_2Cl), 5.56–5.72 (m, 1H, $\sum J$ = 6.9 Hz, Me*CH*), 6.21 (dd, 1H, H-4, $J_{3,4}$ = 3.96 Hz, $J_{4,5}$ = 2.65 Hz, H-4), 6.98 (dd, 1H, $J_{3,4}$ = 3.96 Hz, $J_{3,5}$ = 1.88 Hz, H-3), 7.08 (t, 1H, H-5); MS *m*/*e* (rel intensity) 241 (83), 206 (31), 198 (93), 170 (47), 164 (27), 136 (37), 94 (100). This compound was not further characterized.

(*R*)-1-(5-Iodopentan-2-yl)-2-butyrylpyrrole (53). This compound was prepared from **52** in 76–86% yield in the same manner as described for the synthesis of **4a–f**, etc. After purification by column chromatography on silica gel using hexane–ethyl acetate (9:1) as the eluting solvent, **53** was obtained as an oil; $[\alpha]^{20}_D$ 51.3° (*c* 1.3, MeOH); HRMS calcd for $C_{13}H_{20}INO$ 333.0588, found 333.0588.

(*R*)-3-Butyryl-5-methyl-5,6,7,8-tetrahydropyrrolo[1,2-*a*]pyridine (42). The general procedure was used to effect the cyclization of **53** to **42**. The crude material was purified by column chromatography on silica gel using hexane–ethyl acetate (9:1) to elute the product as an oil: $[\alpha]^{20}_D$ −176° (*c* 5.0, MeOH); IR ($CHCl_3$) 1633 cm^{-1}; ^{1}H NMR (200) δ 0.98 (t, 3H, J = 7.4 Hz, *Me*CH_2), 1.35 (d, 3H, J = 6.5 Hz, 5-Me), 1.63–2.10 (m, 6H), 2.56–3.01 (m, 2H), 2.71 (t, 2H, J = 7.4, $COCH_2$), 5.23–5.39 (m, 1H, H-5), 5.88 (d, 1H,

(50) Brandange, S.; Lundin, C. *Acta Chem. Scand.* **1971**, *25*, 2447.

J = 4.07 Hz, H-2 or H-3), 6.99 (d, 1H, J = 4.07 Hz, H-3 or H-2); HRMS calcd for $C_{13}H_{19}NO$ 205.1467, found 205.1466.

(*R*)-3-Thiobutyryl-5-methyl-5,6,7,8-tetrahydropyrrolo-[1,2-*a*]pyridine (54). A solution of the ketone **42** (0.100 g, 0.49 mmol) and Lawesson's reagent (0.236 g, 0.60 mmol) was heated at reflux temperature in anhydrous THF (5 mL) for 4 h. Hexane (10 mL) was added, the mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (5 g) using hexane–ethyl acetate (95:5) to elute the thione **54** as a very unstable oil (0.099 g, 92% yield): ^{1}H NMR (200) δ 0.99 (t, 3H, J = 7.35 Hz, $MeCH_2$), 1.32 (d, 3H, J = 6.35 Hz, 5-Me), 1.76–2.10 (m, 6H), 2.62–3.01 (m, 2H, 8-CH_2), 3.19 (t, 2H, J = 7.8 Hz, $CSCH_2$), 5.96 (d, 1H, J = 4.38 Hz, H-1), 6.09–6.23 (m, 1H, H-5), 7.20 (d, 1H, J = 4.38 Hz, H-2). This compound was not characterized further.

(*R*)-3-Butyl-5-methyl-5,6,7,8-tetrahydropyrrolo[1,2-*a*]pyridine (55). A suspension of W-2 Raney Nickel (0.3 g) in methanol (8 mL) containing the thioketone **54** (0.090 g, 0.40 mmol) was stirred at room temperature until TLC had indicated the disappearance of the thione (1.5 h). The mixture was filtered through Celite, the filtrate was evaporated *in vacuo*, and the residue was purified by column chromatography on neutral alumina (act III, 5 g) using hexane to elute the unstable product **55** (0.068 g, 87% yield) as an oil: $[\alpha]^{20}_D$ −15.6° (*c* 1.1 MeOH); ^{1}H NMR (200) δ 0.95 (t, 3H, J = 7.2 Hz, $MeCH_2$), 1.21–2.10 (m, 8H), 1.31 (d, 3H, J = 6.5 Hz, 5-Me), 2.52 (t, 2H, J = 7.8 Hz, CH_2-Pr), 2.59–2.93 (m, 2H, 8-CH_2), 4.20–4.34 (m, 1H, H-5), 5.75 (d, 1H, J = 3.34 Hz, H-1 or H-2), 5.85 (d, 1H, J = 3.34 Hz, H-2 or H-1); MS *m/e* (rel intensity) 191 (47), 162 (50), 148 (100). This compound was used directly in the next step.

Catalytic Hydrogenation of 55. Synthesis of (−)-Monomorine (40) and Diastereomers 56–58. A solution of the ketone **55** (0.095 g, 0.5 mmol) in methanol (5 mL) containing suspended 5% Rh–Al_2O_3 catalyst (0.045 g) was hydrogenated at 55 psig for 12 h. The mixture was filtered through Celite and the filtrate was evaporated *in vacuo*. The residue was then taken up in hexane–ethyl acetate (7:3) and filtered through a pad of act. III neutral alumina (0.5 g). Evaporation of the solvent gave the mixture of bases (0.075 g, 76% yield) which by GLPC [30-m DB-5MS capillary column (0.254 mm diameter); He flow rate 1 mL/min; 100 °C for 5 min then 2.5 °C/min increase for 37 min] was a 33:40:24:3 mixture of (−)-monomorine (**40**), **56**, **57**, and **58**, respectively. This mixture was subjected to column chromatographic separation on neutral alumina (act. II) using hexane–ethyl acetate (98:2) as the eluting solvent. In this way there were obtained pure samples of (−)-monomorine (0.009 g), the 3*R*,5*R*,9*S* compound **56** (0.011 g), the 3*R*,5*R*,9*R* compound **57** (0.007 g), and the 3*S*,5*R*,9*S* compound **58** (0.002 g) as well as mixtures of **40** and **56** (0.021 g), and **56** and **57** (0.018 g). The ^{13}C NMR spectra of these bases are found in Table 5. All of the compounds were obtained as oils.

(−)-Monomorine (40): $[\alpha]^{20}_D$ −26.4° (*c* 1.0, hexane), lit.[26] $[\alpha]^{20}_D$ −35.8° (*c* 1.35, hexane); HRMS calcd for $C_{13}H_{25}N$ 195.1987, found 195.1982.

(3*R*,5*R*,9*S*)-Diastereomer (56): $[\alpha]^{25}_D$ −24.5° (*c* 0.29, hexane); ^{1}H NMR (200) δ 0.85–0.98 (m, 6H), 1.15–1.85 (m, 16H), 2.32–2.53 (m, 2H), 3.30–3.45 (m, 1H); HRMS calcd for $C_{13}H_{25}N$ 195.1987, found 195.1982.

(3*R*,5*R*,9*R*)-Diastereomer (57): $[\alpha]^{25}_D$ −85.0° (*c* 0.2, MeOH), lit.[37] $[\alpha]^{16}_D$ 65° (*c* 0.41, MeOH); HRMS calcd for $C_{13}H_{25}N$ 195.1987, found 195.1984.

(3*S*,5*R*,9*S*)-Diastereomer (58): $[\alpha]^{25}_D$ 33.1° (*c* 0.1, MeOH); ^{1}H NMR (200) δ 0.89 (t, 3H, J = 7.0 Hz, CH_2Me), 1.10–2.09 (m, 16H), 1.16 (d, 3H, J = 7.0 Hz, 5-Me), 2.19–3.00 (m, 2H), 3.23–3.36 (m, 1H); HRMS calcd for $C_{13}H_{25}N$ 195.1987, found 195.1987.

Acknowledgment. The authors wish to gratefully acknowledge much spirited discussion with Dr. L. A. Flippin on many aspects of this research.

Note Added in Proof: While this manuscript was being examined by the referees, we have found that catalytic hydrogenation of **42** under recently described conditions (10% Pd–C/55 psig/MeOH–catalytic H_2SO_4; Bond, T. J.; Jenkens, R.; Ridley, A. C.; Taylor, P. C. *J. Chem. Soc. Perkin Trans 1* **1993**, 2241) occurs slowly (7 days) at room temperature to give an 86:14 mixture of (−)-monomorine (**40**) [$[\alpha]^{20}_D$ −34.1° (*c* 0.17, hexane)] and **57** in 74% yield.

Supplementary Material Available: Spectral data for **2b–e**, **3a–f**, **4a–f**, **5a–f**, **6b,d,e**, **7a,f**, **20–22**, **28**, **40**, **48**, **53**, and **57** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.